IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

MASSFELDER et al.		Atty. Ref.:	**3665-133**
Serial No.	**10/520,085**	Group:	**1643**
Filed:	**January 5, 2005**	Examiner:	**Gussow**

For: **USE OF PTHRP ANTAGONISTS FOR TREATING RENAL CELL CARCINOMA**

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

RULE 132 DECLARATION

I, Mustapha OULAD ABDELGHANI, do hereby declare and say as follows:

1. I have reviewed the above-identified application. I have also considered the documents listed herein.

2. I am currently a Research Engineer (IR1, INSERM), in charge of the monoclonal antibody facility at the IGBMC (ILLKIRCH, FRANCE). I hold a Ph D from University of Burgundy, DIJON, FRANCE, earned in (1991).

3. I have been advised by the applicants' French representative that the U.S. Patent Office official in charge of the examination of the application has asserted that the specification allegedly fails to describe the use of an anti-PTHrP (34-53) antibody. I have been advised by the applicants' French representative that the U.S. Patent Office official in charge of the examination of the application has asserted that the specification only describes the use of the Ab-2 anti-PTHrP (34-53) antibody which was

available from Oncogene and was used in the specification to exemplify the disclosure of the application.

4. For the reasons detailed herein, I believe that one of ordinary skill in the art will appreciate that the applicants described the general use of an anti-PTHrP (34-53) antibody as an antagonist for treating a kidney cancer and were in possession of such a method as evidenced by the disclosure of the above-identified specification.

5. One of ordinary skill will appreciate that an "anti-PTHrP (34-53) antibody" refers to an antibody that binds residues 34-53 of PTHrP. Evidence of such terminology may be found, for example, in the following:

(1) Okada et al "Immunohistochemical Localization of Parathyroid Hormone-related Protein in Canine Mammary Tumors" Vet Pathol 34: 356-359 (1997) (describing an antibody to "PTHrP (1-36)" (page 356 right column), the use of a "commercially available rabbit-derived anti-PTHrP (34-53) antibody" (id.), and the N-terminus (1-36) and midregion (36-111) of PTHrP);

(2) Verheijen et al, "Parathyroid hormone-related peptide (PTHrP) induces parietal endoderm formation exclusively via the Type I PTH//PTHrP receptor" Mechanisms of Development 81 (1999) 151-161 (describing the N-terminus of PTHrP as "PTHrP (1-34)" (see page 151, left column), the use of the N-terminal fragment "PTHrP(1-34)" and full length version "PTHrP(1-141)" (see page 152, right column), and fragments spanning amino acids 67-86, 67-94 and 107-139 as "PTHrP(67-86)", PTHrP(67-94)" and "PTHrP(107-139)", respectively (see page 153, left column and Figure 1, and the "Materials" section on page 158 which describes the source of peptides and antibodies));

(3) Thorikay et al., "Synthesis of a gene encoding parathyroid hormone-like protein-(1-141): purification and biological characterization of the expressed protein" Endocrinology, Vol 124, 111-118 (1989) (abstract) (describing "PTHLP" as a 141 amino acid protein designated "PTHLP-(1-141)");

(4) Fenton et al., "A carboxyl-terminal peptide from the parathyroid hormone-related protein inhibits bone resorption by osteoclasts." Endocrinology. 1991 Oct;129(4):1762-8 (Abstract) (describing a carboxy fragment of PTHrP as "PTHrP-(107-139)");

(5) Santos et al "Up-regulation of parathyroid hormone-related protein in folic acid-induced acute renal failure" Kidney International, vol. 60 (2001), pp 982-995 (describing "anti-PTHRP antibody Ab-2 (Oncogene, Uniondale, NY, USA), [as] recognizing the sequence 34 to 53 of human and rat PTHrP" on page 983);

(6) Garcia-Ocana et al "Cyclosporine increases renal parathyroid hormone-related protein expression in vivo in the rat" transplantation, vol 65, 860-863, No. 6, March 27, 1998 (describing "anti-PTHRP antibody Ab-2 (Oncogene, Uniondale, NY), [as] recognizing the sequence (34-53) of human and rat PTHrP" on page 861); and

(7) Richard, et al. "Humoral Hypercalcemia of Malignancy, Severe Combined Immunodeficient/Beige Mouse Model of Adult T-Cell Lymphoma Independent of Human T-Cell Lymphotropic Virus Type-1 Tax Expression" Am J Pathol. 2001 June; 158(6): 2219–2228 (describing "polyclonal rabbit anti-PTHrP (PTHrP amino acids 34 to 53) (1:100, Ab-2, Oncogene Research Products, Cambridge, MA)").

Each of the above-noted references describes fragments of PTHrP by the amino acid positions, in parentheses, as recited in the above-identified application.

The following references, for example, make similar reference to fragments of PTHrP:

(A) Burtonet al., "Parathyroid hormone related peptide can function as an autocrine growth factor in human renal cell carcinoma" 1990, Biochemical and Biophysical Research Communications, Vol. 167, No. 3, pages 1134-1138;

(B) Ogata et al (EP1197225);

(C) Hoare et al "Specificity and stability of a new PTH1 receptor antagonist, mouse TIP(7-39)" Peptides, 2002, vol 23, No. 5, pp 989-998; and

(D) Sato et al (U.S. Patent No. 6,903,194).

6. .Sato et al describes "Humanized anti-PTHrP (1-34) Antibody" in Figures 13 and 14. Moreover, Sato et al describes the use of a fragment "[PTHrP(1-34)]" as an antigen to produce antibodies as follows:

> "PTHrP used for the immunization of animals includes peptides having the whole or part of the amino acid sequence of PTHrP prepared by recombinant DNA technology or chemical synthesis, and PTHrP derived from supernatants of cancer cells causing hypercalcemia. For example, a peptide [PTHrP(1-34)] comprising the 1st to 34th amino acids of the known PTHrP (Kemp, B. E. et al., Science (1987) 238, 1568-1570) may be used as the antigen." See column 7, lines 48-55 of Sato.

Further, Sato describes antibodies binding human PTHrP as "anti-human PTHrP antibodies" and generally antibodies which bind PTHrP as "Anti-PTHrP Antibody". See column 10, last line, column 22, line 56, and, for example, column 23, lines 25 and 37-38 of Sato.

7. One of ordinary skill in the art will appreciate that "an anti-PTHrP (34-53) antibody" is a general recitation of an antibody which binds to the fragment of PTHrP spanning amino acids 34-53.

8. The above-identified specification describes the following as examples of an anti-PTHrP antibody which may be an antagonist according the disclosure: the anti-PTHrP(1-34) antibodies (human, rat) of Bachem (Bachem Biochimie Sarl, Voisins-le-Bretonneux, France), the anti-PTHrP(34-53) antibody (Ab-2, human) of Oncogene (France Biochem, Meudon, France), the antibody #23-57-137-1 (described in particular in the patent application EP1197225) and the anti-PTHrP(107-139) antibody (human) obtained by conventional methods of antibody preparation. See page 9, lines 10-15 of the above-identified specification. One of ordinary skill in the art will further appreciate from, for example, page 21, line 31 ("anti-PTHrP (34-53)"), page 17, lines 25-28 ("The anti-PTHrP(34-53) antibody (Ab-2, human) was obtained from Oncogene (France Biochem, Meudonm France) and the anti-PTHrP(107-139) antibody (human) was a gift of Dr. P. Esbrit (Fundacion, Jimenez Diaz, Madrid, Spain)") and page 27, line 1 ("Int. region: anti-PTHrP (34-53) antibody (Ab-2, Oncogene) 2 µg/ml") of the specification, that the above-identified specification describes the use of anti-PTHrP antibodies from a number of sources as exemplifications of anti-PTHrP antibodies which bind to the amino acid fragment described numerically in parentheses (i.e., fragments of PTHrP spanning amino acids 34-53 and 107-139 in the above-noted passages).

9. The above-identified specification describes in the background section the previous experiences in the art with anti-PTHrP antibodies and that the above-identified application provides a therapy based on the use of PTHrP antagonists to treat patients

affected by clear cell carcinoma (CCC). See page 5, last paragraph of the specification. PTHrP antagonists are described in specification as including compounds which decrease the biological effect or effects of PTHrP and can include a compound binding the PTHrP receptor which partially or wholly inhibits binding of PTHrP to its receptor. These antagonists are described as including peptides of PTH or PTHrP comprising a substitution or deletion of at least one amino acid of the sequence of the PTH and or the PTHrP, or a partial sequence of the PTH or PTHrP peptides, optionally comprising a substitution or a deletion of at least one amino acid of their sequence. See page 7, lines 3-14 of the specification.

10. The above-identified specification further describes that specific examples of antagonist compounds binding the PTHrP receptors according to the invention include PTHrP (3-34), PTHrP (7-34), PTHrP (8-34), PTHrP (9-34), PTHrP (10-34), the amides or variants thereof. Variants present a replacement, a deletion or an addition of at least one amino acid such as in particular (Asn10, Leu11, D-Trp12) PTHrP (7-34) amide (human or murine). One of ordinary skill in the art will appreciate that "PTHrP(3-34)", for example, is a peptide containing the amino acid sequence of amino acids 3 to 34 of the PTHrP peptide. The specification further describes that among the above-described polypeptides, are also included those which present a deletion, a substitution, an addition or an insertion of at least one amino acid of the peptide sequence of PTH or PTHrP and which have an antagonist activity in respect of PTHrP. The specification further describes a derivative of TIP (tuberoinfundibular peptide) as a PTHrP antagonist, such as truncated peptides of TIP(1-39) (tuberoinfundibular peptide 1-39), in particular TIP(7-39) and its derivatives which have been described as

powerful RPTH1 antagonists (Hoare et al, Peptides 23 : 989-998, 2002). See page 7, lines 14-26 of the specification. The specification further describes that the PTHrP antagonist according to the application may be a non-peptidic compound. See page 7, lines 27-29 of the specification.

11. The above-identified specification describes that a PTHrP antagonist according to the description can be a compound binding a ligand of the PTHrP receptor, thereby partially or even totally inhibiting the binding of PTHrP to its receptor. This compound can be selected from anti-PTHrP antibodies and, more preferably, a humanised anti-PTHrP antibody. See page 7, lines 30-33 of the specification.

12. The specification describes that a PTHrP antagonist according to the invention can be a compound increasing the presence of active VHL, thereby decreasing the biological effect or effects of PTHrP, such as a product of the tumour suppressing gene VHL, which can be obtained in particular by gene therapy. The specification further describes that a PTHrP antagonist according to the invention can be a compound reducing the expression of PTHrP. This compound can bind mRNA or the gene of PTHrP, inhibiting, partially or even totally the expression of PTHrP. This compound can be for example an antisense oligonucleotide of PTHrp, a RNAi, a transcription factor repressing the expression of the PTHrP gene or a compound decreasing the stability of the mRNA of PTHrP. See page 8, lines 1-11 of the specification.

13. The specification describes that several kinds of PTHrP antagonists such as defined throughout the specification can be used for the treatment of kidney cancer. The specification describes, for example, a method of treatment including gene therapy

and the administration of a PTHrP antagonist such as an antagonist of the PTHrP receptor or an anti-PTHrP antibody. See page 8, lines 12-17 of the specification.

14. Antagonists are further described in the specification as including a compound, such as an anti-PTHrP antibody, which inhibits the binding of a ligand, such as PTHrP, to a PTHrP receptor. Examples of anti-PTHrP antibodies include antibodies such as a humanised antibody, a human antibody, a chimeric antibody, an antibody (such as the antibody #23-57-137-1 (which binds PTHrP(1-35) see Esaki et al "The selection of therapeutic antibodies by kenetic analysis" Biocore Journal – Number 2 2002, pages 7-8)) obtained from a hybridoma (such as the hybridoma #23-57-137-1) or a fragment of an anti-PTHrP which inhibits binding of a ligand to the receptor and/or a modified form of such a fragment. The antibody can be polyclonal or monoclonal. See page 8, lines 23-31 and page 9, lines 4-9 of the specification.

15. The above-identified specification describes the following as examples of an anti-PTHrP antibody which may be an antagonist according the disclosed invention: the anti-PTHrP(1-34) antibodies (human, rat) of Bachem (Bachem Biochimie Sarl, Voisins-le-Bretonneux, France), the anti-PTHrP(34-53) antibody (Ab-2, human) of Oncogene (France Biochem, Meudon, France), the antibody #23-57-137-1 (described in particular in the patent application EP1197225) and the anti-PTHrP(107-139) antibody (human) obtained by conventional methods of antibody preparation. See page 9, lines 10-15 of the above-identified specification.

16. The specification further describes the use of fragments of PTHrP as antigens to produce anti-PTHrP antibodies in mammals, such as a rodent (e.g., mouse, rat or hamster), a rabbit or a monkey. See page 9, line 29 through page 10, line 4 of

the specification. Production of anti-PTHrP antibodies from human cells is also described. See page 11, lines 16-26 of the specification. Recombinant anti-PTHrP antibodies are described. See page 11, line 27 through page 12, line 2 of the specification.

17. Page 14, lines 12-14 of the specification describes the results of Figure 4 of the specification as showing the "effect of the antibodies against the various regions of PTHrP on the proliferation of the tumor cells 786-0 *in vitro* measured by the number of cells... ". Figure 4 describes these "regions" as "N-term", "Region Int" and "C-term". The specification further defines these regions as follows (see page 26, line 33 through page 27, line 2 of the specification):

"N-term: anti-PTHrP(1-34) antibody (Bachem) 1.5 µg/ml

Int. region: anti-PTHrP (34-53) antibody (Ab-2, Oncogene) 2 µg/ml

C-term: anti-PTHrP(107-139) antibody (P. Esbrit, Madrid, Espagne) 5 µg/ml" .

18. One of ordinary skill in the art will appreciate that Figure 4 of the specification describes results of antibodies binding to regions of PTHrP generally, which are described as being applicable to any anti-PTHrP antibody binding the noted region of PTHrP, and are considered a demonstration of the applicants disclosure and description of the invention.

19. Figure 6 of the specification similarly describes results relating to anti-PTHrP antibodies which bind to regions "N-term" (i.e., PTHrP(1-34)), "Region Int." (i.e. PTHrP (34-53)), and "C-term" (i.e., PTHrP(107-139)) of PTHrP. The corresponding description of the specification (i.e., page 27, lines 14-23) describes the general applicability of the

results of Figure 6 as representing "the effect of the antibodies directed against the different regions of PTHrP on the proliferation of the UOK-126 tumor cells *in vitro* ...".

20. One of ordinary skill in the art will appreciate that Figure 6 of the specification describes results of antibodies binding to regions of PTHrP generally, which are described as being applicable to any anti-PTHrP antibody binding the noted region of PTHrP, and are considered a demonstration of the applicants invention.

21. Figure 8 of the specification similarly describes results relating to anti-PTHrP antibodies which bind to regions "N-term" (i.e., PTHrP(1-34)), "Region Int." (i.e. PTHrP (34-53)), and "C-term" (i.e., PTHrP(107-139)) of PTHrP. The corresponding description of the specification (i.e., page 28, lines 1-12) describes the general applicability of the results of Figure 8 as representing "the effect of the antibodies directed against the different regions of PTHrP on the proliferation of the UOK-128 tumor cells *in vitro* ...".

22. One of ordinary skill in the art will appreciate that Figure 8 of the specification describes results of antibodies binding to regions of PTHrP generally, which are described as being applicable to any anti-PTHrP antibody binding the noted region of PTHrP, and are considered a demonstration of the applicants invention.

23. One of ordinary skill in the art will appreciate, from the whole of the specification, that the applicants were in possession of the claimed invention, relating to the use of an anti-PTHrP (34-53) antibody. The specification is not limited to the specific Ab-2 anti-PTHrP (34-53) antibody used in the examples.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and

further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Signed this 27th day of November, 2008.

(Signature)_____

(print name) Mustapha OULAD ABDELGHANI